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EXAMINER

EWOLDT, GERALD R

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1644

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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DETAILED ACTION

1. Applicant's amendment, remarks, and IDS, filed 8/19/08 are acknowledged.
2. Claims 2, 4, 8-10, 24-36, and newly added Claims 37 and 38 are pending and being acted upon.
3. In view of Applicant's amendment, the previous rejection under the first paragraph of 35 U.S.C. § 112 for the introduction of new matter into the claims has been withdrawn.
4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 2, 4, 8-10, 24-36, and newly added Claims 37 and 38 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could be used for expressing a molecule on a cell, said method comprising photochemical internalization wherein the molecule is sufficient to generate an immune response (Claim 24), more specifically CTL mediated cell killing (Claim 2), for the reasons of record. Additionally, the specification provides insufficient evidence that the claimed method could be used for the newly claimed limitations of Claim 37 wherein the peptide and photosensitizing agents employed in the claimed method are administered directly to a patient.

As set forth previously, the breadth of the claims, in light of the limited disclosure of the specification, would not allow one of skill in the art to practice the invention as broadly claimed without an undue amount of experimentation.

First note that it is clear that the photochemical method (employing certain disclosed agents) of the instant application (and the prior art) can be used to internalize exogenous molecules. The method of the instant claims,

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however, requires more. The claimed method requires the surface presentation of a sufficient amount of the internalized molecule to generate an immune response.

It is well-known in the immunological arts that only certain antigen presenting cells are capable of presenting antigens and generating an immune response. See, for example, Janeway et al. (1994) wherein it is taught that in addition to antigen presentation, costimulation that can only be provided by B cells, macrophages, or dendritic cells, is required for the generation of an immune response. Accordingly, it appears that the method of Claims 2-5 and 7-11, employing any cell capable of photochemical internalization, could not be performed without an undue amount of experimentation.

Further regarding the breadth of the claims, the specification discloses only the actual use of AlPcS_{2a} and TPPS_{2a} as photochemical internalization agents. Claims 2-7 and 9-11 comprise either no limitations regarding photochemical internalization agents, or as in the case of Claim 7, are drawn to whole classes of agents. The disclosure of two related species of agents cannot be considered to be reasonably sufficient to enable the method of the instant claims to be performed with any of the essentially unlimited number of disclosed families of chemicals without an undue amount of experimentation.

Finally, it remains the Examiner's position that the disclosure of the specification does not sufficiently demonstrate the required limitation that the claimed method be capable of inducing sufficient MHC class I presentation of an antigen to generate an immune response. As set forth previously, the specification fails to disclose any actual Class I MHC presentation. Indeed, the only experiment which might demonstrate any sort of surface presentation, Example 3, clearly demonstrates the opposite, the triangles of Figure 4 show a lack of antigen on the surface of the cells.

Example 2 was discussed in the Office action of 1/09/07. Regarding Example 2, said example was discussed in the actions of 4/01/05 and 11/29/05:

In regards to Example 2, the methods of the example are not the methods of the instant claims, nor are they representative of the scope of the methods of the instant claims. In the example, a single cell type is loaded with a particular antigen; said loaded cell is then used in a CTL ⁵¹Cr release assay. The CTLs employed in a ⁵¹Cr assay are primed/activated CTLs and are not representative of the generation or stimulation of an immune response, i.e., the method of the instant claims. See, for example, Janeway et al. (1994) wherein one of the fundamental rules of cellular immunology is taught, i.e., that the generation of an immune response from naïve T cells requires professional APCs. Clearly then, the ⁵¹Cr assay of Example 2 employs primed/activated CTLs and does not comprise the generation or stimulation of an immune response. Note also that the specification discloses that the assay of Example 2 is the assay of Fossum et al. (1995) in which primed CTLs were employed. Accordingly, it remains the Examiner's position that given the breadth of the claimed method, i.e., the employment of *any* cell type in the production of cells capable of generating an immune response (in defiance of one of the fundamental concepts of cellular immunology), the specification provides insufficient support and is not enabling.

Further, because the example comprises no appropriate controls, the skilled artisan would know that no conclusions could be drawn based on the disclosed results. Regarding Claim 6, first note that the limitations of the claim apply only to Claim 6, regardless, neither all types of lymphocytes nor all types of

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cancer cells are capable of the stimulation/generation of any/all types immune responses as are encompassed by the instant claims.

Also note that the example is not representative of the generation of cytotoxic T cell killing which encompasses the generation of activated T cells from naïve T cells.

As set forth previously, the declaration of Inventor Hogset was considered in the Office action of 2/10/03:

In regards to the 1.132. declaration of Inventor Hogset, it is now disclosed that factors not disclosed in the specification are critical to the functionality of the claimed method. "Whether or not cell death results after photochemical treatment is principally dependent on two factors. Firstly the amount of toxic substances generated by the photosensitizing compounds on exposure to light and secondly, the presence and toxicity of molecules which are internalized during this process." Again, given the lack of guidance in the specification, the claimed method must then be considered highly unpredictable and requiring of undue experimentation in view of these newly disclosed factors.

Regarding the photosensitizing compounds and exposure to light, while specific photosensitizing compounds are disclosed and claimed, no specific concentrations of said photosensitizing compounds (other than that used in Example 2) are claimed nor disclosed. Clearly, this parameter must be considered in that too much photosensitizing agent will induce cell death. Even more importantly, the declaration discloses that, whereas "the level of toxic substances which are generated may be controlled by the selection of the photosensitizer to be used, [and] the dose of that photosensitizer, but most crucially, the time of illumination which leads to increasing levels of the toxic substances" [must be considered]. The declaration goes on to demonstrate that too little light will not induce internalization while too much light kills the cells. Again it is clear, particularly in regards to the light parameters, i.e., source (wavelength), intensity, and duration, that the specification provides insufficient support for the claimed method. Again, given the lack of guidance in the specification, the claimed method must then be considered highly unpredictable and requiring of undue experimentation.

Finally, regarding the antigen to be internalized, the instant declaration states "the toxicity resulting from the molecules which are introduced may be readily controlled by selecting an appropriate toxic or non-toxic molecule for transfer, depending on the desired end use." The specification discloses however, that essentially any antigen can be used including "all manner" of pathogenic antigens, as well as peptides involved in diseases ranging from cancer to multiple sclerosis. The specification fails, however, to disclose how to "appropriately select" among the toxic and non-toxic molecules. Indeed, even the instant post-filing declaration fails to indicate how such a selection is to be made; it only indicates that said selection is essential, which once again demonstrates the lack of guidance in the specification.

Regarding toxicity, the specification fails to even mention this possible problem. Said problem was brought to light only in the Inventor's own post-filing declaration. Clearly then, the specification cannot be enabling in this regard.

Applicant alleges that the relevance of Example 2 has been dismissed by the Examiner.

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Applicant's allegation is clearly not true as the Example has been considered and addressed multiple times. The Example has not been found enabling for the breadth of the claimed method as set forth above.

Applicant argues that the generation of primed CTLs is not necessary, submitting Salgaller et al. (1996) in support.

The teachings of Salgaller et al. are not in the scope of the method of the instant claims. Salgaller et al. preselected specific peptides from a well-known and previously characterized tumor associated antigen (gp100) based on recognition in culture by tumor infiltrating lymphocytes. Note that only responding cultures are discussed, i.e., there is no discussion of how many cultures failed to respond to stimulation. Contrast this to the method of the instant claims which simply recite a method of inducing CTLs or a generic immune response to any peptide under any, including *in vivo*, conditions. Accordingly, the reference cannot provide support for the broad method of the instant claims.

Applicant cites Valmori et al. (1998) as teaching the generation of primed CTLs.

None of the instant claims recite any method steps for the priming of CTLs. Accordingly, it is unclear how the reference supports the claimed method.

Applicant argues that cancer vaccines are known in the art. And that down regulation of MHC Class I is not a universal phenomenon.

Applicant's argument is noted, but the fact remains that the instant specification fails to address the issue of down regulation of MHC Class I by some tumors.

Applicant's arguments, filed 8/19/08 have been fully considered but they are not persuasive. Applicant again cites Example 2 as enabling the claimed invention.

Example 2 has been addressed throughout the lengthy prosecution of this application. It would serve no purpose to reiterate why said example is not representative of the scope of the claimed invention except to note that even Applicant acknowledges that said example shows just, "one type of immune response" (instant remarks, page 8). As set forth previously, said, "one type of immune response" comprises merely the simplest and most easily induced type of response (memory) and it does not enable the claimed response that encompasses the activation of a naive cytotoxic T cell (CTL) response as well as the induction of said response by cells other than antigen presenting cells (in certain claims).

Applicant argues that the examiner is requiring a reduction to practice.

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No such reduction to practice has been required. A specification enabling of the reasonable scope of the claimed invention is, however, required.

Applicant argues, "as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied."

The point is that the specification fails to show, "a reasonable correlation to the entire scope of the claim". Particularly note Applicant's acknowledgement that the specification must demonstrate the enablement of the "*the entire scope of the claim*". That the specification fails in this required showing is the Examiner's very argument.

Applicant argues that the specification shows, "the user of primed cytotoxic T cells (CTL)" (instant remarks, page 10).

Note that Applicant appears to acknowledge that the specification does *not* show the use of non-primed (naïve) CTL. As set forth in previous Office actions, the induction of a naïve CTL response requires far more than the induction of a memory (primed) CTL cell response.

Applicant argues that the specification is not required to present *in vivo* data (presumably as enablement for the new *in vivo* method of Claim 37) arguing that "appropriate *in vitro* data is acceptable. Applicant reiterates the minimal teachings of the disclosure and the prior art, finds them enabling, and concludes, "The only question which would seem to remain is whether a suitable response would be achieved *in vivo*."

Given that the data of the specification is not enabling for *in vitro* methods, how then can said limited data be considered to be enabling for infinitely more complex *in vivo* methods? *In vivo* methods require considerations of dosage, bioavailability (including bioaccessibility and bio half-life) as well as additional toxicity issues. Consider, as a single example, the Inventor's own admission (in his 1.132 declaration referenced above) that the exposure of the photosensitizing agent to activating light comprises a critical factor. How would the invention be controlled to administer the necessary level of light to internal organs while limiting the level of light administered to surface areas of the patient?

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Applicant again cites Salgaller et al. and Valmori et al. (both of record).

As set forth above, the references do not enable the claimed method which encompasses (at its broadest) the generation of a naïve CTL response by simply administering (or contacting) cells with any antigen and vast array of photosensitizing agents.

As an example of the specification's lack of enabling teachings, consider Applicant's argument at pages 13-14 that, "the specification clearly describes how to use the photosensitizing agents and light irradiation properly in the methods of the invention", citing page 14 of the specification. A review of the specification merely discloses that, "photosensitising agent the potency/ability to disrupt membranes on irradiation, should also be taken into account". An enabling specification requires more than the identification of a potential problem, it requires a potential solution for the problem.

Applicant argues that the examiner has overstated the issues of toxicity and MHC Class I downregulation.

Applicant is reminded that it was the Inventor, in his own 1.132 declaration, that raised the issue of toxicity. Regarding MHC Class I downregulation, it was cited merely as a example of one of the myriad of issues *not* addressed in the instant specification.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 2, 4, 8-10, 24-36, and newly added Claims 37 and 38 stand/are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/07432 (IDS).

As set forth previously, W096/07432 teaches a method of expressing [now presenting an antigenic molecule on the surface of a viable cancer cell, said method comprising:

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contacting said cell *in vitro* [and *ex vivo*] with said antigenic molecule [now peptide] (including a vaccine component, a molecule capable of stimulating an immune response, and a peptide, also including an antigen bound to a carrier molecule) and with a photosensitizing agent (a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, and tetracycline, including TPPS₄, TPPS_{2a}, and AlPcS_{2a}, also including a photosensitizing agent bound to a carrier molecule), wherein said molecule and said agent are each taken up into an intracellular membrane-restricted compartment of said cell; and irradiating said cell with light of a wavelength effective to activate the photosensitizing agent, such that the membrane of said intracellular compartment is disrupted, releasing said molecule into the cytosol of the cell, without killing the cell by irradiation, wherein, said released antigenic molecule, or a part thereof of sufficient size to generate an immune response, is subsequently presented on the surface of said cell by a class I MHC molecule (see particularly the claims). Note that reference does not specifically state that the method results in the cell surface expression of the antigen in MHC Class I, however, the reference teaches the same steps as those of the instant claims, thus, said same steps would inherently result in the same outcome, i.e., the claimed method of the expressing an antigenic molecule on the surface of a viable cell.

Note that the reference further teaches the *in vivo* administration of and antigen and photosensitizing agent (page 6), thus, new Claim 37 has been included in the rejection.

As set forth previously, Applicant's arguments, filed 11/02/07 have been fully considered but they are not persuasive. Applicant argues that the claimed method is directed to a method of presenting an *antigenic peptide* on the surface of a *viable* cancer cell or antigen presenting cell whereas the method of the prior art is limited to delivery of *active, whole molecules* to the *cytosol* of cells. Applicant then discusses the Examples in detail.

While Applicant cites the Examples, the reference further teaches the delivery of peptides (Claim 2) which would be antigenic depending on the context, *in vivo* (page 6). Further note that essentially all of the cells described and used in the reference are cancer cells. The result of the delivery of peptides *in vivo* by the identical methods would necessarily be the same result achieved by method of the instant claims.

Applicant's arguments, filed 8/19/08 have been fully considered but they are not persuasive. Applicant argues that the reference, "only discloses photochemical internalization of toxins into cancer cells".

As set forth previously, the reference further discloses the internalization of peptides (Claim 2) which depending on context would be antigenic. The fact that the reference exemplifies the delivery of toxins does not detract from its addition teachings. Further, it is clear that the reference teaches the survival of cells after peptide internalization (see, for example, the Abstract), thus, it is clear that the

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reference encompasses more than the internalization of toxins as Applicant asserts.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara, Ph.D. can be reached on (571) 272-0878.

11. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

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